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TESTOSTERONE SUPPLEMENTATION AND PROSTATE CANCER, CONTROVERSIES STILL EXIST

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Abstract: Late onset hypogonadism is a common condition in aging males. The population of men who can be potentially treated with testosterone supplementation is growing. Controversy that surrounds testosterone replacement therapy is due to generally undefined lower limits of normal testosterone level and high prevalence of hypogonadal symptoms in elderly population and the non-specific nature of these symptoms. Incidence of prostate hyperplasia and occult prostate cancer in elderly are both high. The risk that testosterone treatment would trigger prostate cancer was not fully recognized. The aim of this mini review is to present a risk of carcinogenesis within the prostate related to testosterone treatment.

Keywords: testosterone replacement therapy; late onset hypogonadism; prostate cancer

Controversy surrounds setting a lower limit of normal testosterone. There is also no generally accepted lower limits of normal testosterone level in aging males. It was demonstrated that demographic differences in testosterone level within population of aging male exist (1–3). Testosterone bound to sex-hormone binding protein (SHBG) is tightly bound and thus biologically inactive. Bioavailable and free testosterone is known to correlate better than total testosterone with bone mineral density and muscle strength, but it is difficult to calculate a bioavailable testosterone level for all patients (4). Difficulties can be found when one would classify the clinical syndrome related to late onset hypogonadism. It is due to the high prevalence of hypogonadal symptoms in the aging male population and the non-specific nature of these symptoms. Late onset hypogonadism often coexists with obesity and metabolic syndrome (5, 6). The overall prevalence of late onset hypogonadism varies from 6–9% in men aged 40–70 year old and rises to 15–30% in diabetic and obese men (7, 8). The management of late onset hypogonadism is a testosterone supplementation. Therapy is usually scheduled for a period of a few months or a few years. The population of men who can be potentially treated with testosterone supplementation is growing, due to many factors, like life longevity, patients self-education, commercials and active drug market and finally doctors decisions. The risk of testosterone treatment is still not fully recognized.

The aim of this mini review is to present a risk of carcinogenesis within the prostate related to testosterone treatment.

Hormonal supplementation in elderly, what can be learned from past studies?

There is still considerable controversy concerning influence of testosterone replacement on the prostate gland, because incidence of BPH and occult prostate cancer (PCa) in elderly are both high (9). It is very interesting to compare the effects of hormone replacement therapy in women and men published in 2009. Evidences related to hormone replacement therapy in men look very optimistic. Testosterone, for example, has a wide range of beneficial effects on men's health. It was suggested that androgen deficiency is a risk factor for cardiovascular disease (10). None of 44 controlled trials demonstrated that testosterone therapy for hypogonadism increased prostate cancer risk nor increased tumor aggressiveness (Gleason grade) (11). It has even been advocated that, under a rigorous surveil-

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lance, patients cured of prostate cancer can be treated with testosterone (12). On the other hand, scientific data concerning hormone replacement therapy in women are rather sceptic. The first placebo-controlled trial of hormone therapy with the size and statistical power, did not confirm the hormone-healthy heart hypothesis in women (13). The incidence of invasive breast cancer declined in the United States following a nationwide decrease in the use of hormone replacement therapy (14). Regardless of the duration of use, the formulation, estrogen dose, regimen, progestin type, and route of administration, hormone therapy was associated with an increased risk of ovarian cancer (15). Why there are so huge differences between results of hormone replacement therapy in women and men? The answer probably could be found if the number of published papers on which these two topics were compared. It can be concluded that there are five times as much papers on hormone replacement therapy in women. There are 20,514 papers on hormone replacement therapy women indexed in PubMed, and 5,300 on hormone therapy women and cancer, and 4,132 on hormone treatment and cardiovascular diseases. On the other hand, there are only 5,459 papers on hormone replacement therapy in men and only 950 papers related to cancer and hormone replacement therapy in men, and only 890 analyzing hormone therapy and cardiovascular diseases in men. It can be hypothesized that data relating to hormone replacement therapy in ageing males are scanty. It is difficult to advise a safety long term testosterone therapy for aging males, having in mind that so many papers and long time observation were devoted to hormone replacement therapy in women and the results are still not satisfactory.

Testosterone influences on human prostate

The most interested issue is how testosterone influences on both, epithelial and stromal cell compartments within the prostate? Testosterone is prescribed as a drug which has no influence on lower urinary tract symptoms in men. Does testosterone really not influence on lower urinary tract symptoms in elderly nor men suffering from BPH? To obtain the correct answer one should rather ask; is a human prostate sensitive on testosterone level manipulation or not? Clinical trials have shown that testosterone treatment of hypogonadal men cause growth of the prostate, and increase in PSA within the normal range (16). On the other hand, it was demonstrated that finasteride (inhibitor of dihydrotestosterone, DHT) induces prostate shrinkage, as well as improvement of symptoms in men with BPH. Discontinuation of this therapy induces prostate regrowth, as well as aggravation of obstructive and irritative symptoms generated within lower urinary tract (17). It can be stated that androgens regulate the proliferation of prostate cells within the gland affected with benign prostatic hyperplasia (BPH). Even in a small (44 patients) and short (6 months of treatment) randomized controlled trial it was shown that testosterone treatment had an effect on prostate tissue androgen levels and cellular functions (18). Androgens provide the signal for cell division in normal and enlarged human prostate, as well. A randomized, placebo-controlled trial of finasteride treatment in 18,800 men showed a lower incidence of prostate cancer in the treated group but increased aggressive phenotype of detected cancers (19). Based on these information, it can be stated that our knowledge on carcinogenesis within the human prostate is still obscure. We do not know, if testosterone could trigger cancer or recruit existing malignant lesions to quicker growth or both. It has to be emphasized that androgen receptor expression is higher in cancer when compared to BPH tissue. Prostate cancer is sensitive to testosterone (20). The carcinogenesis within the prostate is a very long process. Relationship between prevalence of prostate cancer and age, support the fact that histological (occult) prostate cancer requires further events to produce clinical disease. The incidence of prostate cancer is rising among elderly. Autopsy studies suggest that prostate cancer may be found in 80% of males over the age of 80 (21). Prostate carcinogenesis takes about 15 to 20 years, but most of trials on testosterone replacement therapy and prostate cancer are designed for duration of 3–5 years, so it is difficult to catch important finding from these studies (11, 18). It is not surprising that controversies on prostate carcinogenesis and testosterone replacement therapy in ageing males still exist. It is not known, if histological (occult) prostate cancer has already undergone or will have to undergo events necessary to be converted into clinical cancer? In other words, it is not known, which of histological (occult) prostate cancers will be converted to clinical one. It is not known, if an epigenetic factor is needed to evoke carcinogenesis. It is not known, how testosterone influences on carcinogenesis in man 40–50 year old, and what effect could be expected after 10 or 20 years following testosterone exposition. The knowledge on testosterone influence and *de novo* carcinogenesis within the human prostate and possible ways of conversions of malignant, occult lesions to clinical cancers is obscure.

Cell senescence, testosterone, and risk of prostate cancer

Androgen replacement therapy in hypogonadal men increases bone density, lean mass, enhances heart muscle, cardiovascular function, and increased prostate volume (17). Many beneficial effects of testosterone therapy in aging males can be observed, so why testosterone therapy is potentially danger in aging male? This phenomenon can be explained based on the function of *P53* gene and P53 protein. Active P53 stops cell division to repair DNA defects. P53 helps to maintain genome stability and prevents carcinogenesis. *P53* is a tumor suppression gene. It is inactive in young cells (progenitor cells), because these cells are characterized by a low number of mutations and consequently, no danger of carcinogenesis is present within them. Young cells have high mitotic rate and young organisms have high regenerative potential. On the other hand, *P53* is active in older cells (differentiated cells) due to a high number of mutations and risk of carcinogenesis. These cells present low mitotic rate connected with the extensive DNA reparation processes. Aging organism is characterized by low regenerative potential and high risk of carcinogenesis (22–24). Testosterone accelerates mitosis of senescent cells containing DNA defects, which results in a lack of DNA repair. It has to be emphasized that some contraindications for testosterone treatment are tumors and proliferative disorders, like prostate cancer, breast cancer, primary liver tumors, and polycythemia (1). The reason for such contraindications is because testosterone is an anabolic hormone, so it has a mitogenic effect on cells. This fact increases a risk of carcinogenesis within the prostate. Presented mechanism is only a potential mechanism responsible for negative influence on the prostate. Testosterone deficiency is an age related phenomenon. Senescence increases risk of malignant disorders. Our knowledge about the rules of machinery contributing in human senescence is limited. We are able only to describe phenomena occurred during human aging and present them as theories. If Richard Dawkins is right that "we are survival machines blindly programmed to preserve genes" than we may be convinced that our organisms are planned to act properly during the period reserved for reproduction, but not during the time of elderly (25). It can be speculated that late onset hypogonadism has to be regarded as a natural mechanism, which protects heredity of defective traits. Late onset hypogonadism is an immanent part of elderly men.

CONCLUSIONS

Both epithelial and stromal cells within the prostate are sensitive for manipulations of testosterone level. Senescence and high mitotic activity increase the risk of cancer. It seems that testosterone increases the risk of prostate cancer and aggravation of lower urinary tract symptoms in BPH patients, but trials dedicated to these relations are too short and recorded data are still scanty.

We hypothesized that there is too early to state that testosterone treatment is a risk free management of late-onset hypogonadism in men.

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